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The role of musculoskeletal ultrasound in predicting treatment plan in rheumatoid arthritis patients

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Abstract
Rheumatoid arthritis (RA) is a progressive autoimmune disease that causes inflammation in the synovial tissue of joints, as well as in both bones and cartilage. Prolonged synovitis leads to joint destruction and deformity. RA is characterized by destructive polyarthritis, extra-articular involvement and autoantibody production, particularly, anti-cyclic citrullinated peptide (Anti CCP) and rheumatoid factor (RF). Musculoskeletal ultrasonography (MSUS) is a more accurate and precise method compared to clinical evaluation for identifying subclinical synovial inflammation. Both at disease onset and throughout the course of the disease to evaluate disease activity. Also, they can detect erosions of smaller joints at an early stage of the illness before the erosion is visible on conventional radiographs which help in earlier diagnosis, treatment and prevention of joint deformities.

Keywords: Rheumatoid arthritis, musculoskeletal ultrasonography, synovitis, erosions

Introduction
Rheumatoid arthritis (RA) is an inflammatory illness marked by persistent inflammation of the joints. It mostly affects the joints in the hands, wrists, feet, knees, elbows, and ankles, causing them to become loose, unstable, and painful. Additionally, deformities may develop. Progressive functional impairment is caused by joint injury that cannot be reversed. RA may also result in tissues inflammation in other regions of the body, including the heart, lungs, and eyes [1]. MSUS has been more popular among rheumatologists due to its non-invasive nature, comparatively lower cost in contrast to MRI, absence of radiation, and ability to provide dynamic evaluation at various joint locations. MSUS provides a more precise evaluation of inflammation of soft tissues compared to traditional clinical testing methods [2]. It is well recognized that inflammation of joints in the US is often seen even when individuals are in a state of clinical remission or have minimal activity of the disease. The significance of subclinical synovitis, namely Power Doppler activity, indicates the likelihood of further radiographic development or clinical flare-up [3]. Effective therapy for RA necessitates the use of technologies that enable timely diagnosis, anticipation of unfavorable prognosis, and assistance in making treatment choices throughout the ongoing monitoring of the illness [4]. Furthermore, MSUS allows intra articular intervention and good visualization of needle placement to the intra-articular compartment, and it permits sampling from the synovial fluid for further work-up [5].

Aetiology of RA
RA is a disease of unknown origin that results from interactions among hereditary susceptibility and environmental factors [6].

1. Genetic predisposition
The human leukocyte antigen (HLA) association in RA is the strongest genetic predisposition to RA especially HLA-DRB1 alleles [7]. The shared epitope refers to the existence of a common amino acid pattern (QKRAA) between positions 70-74 of the DRB1 chain. This motif is connected with a specific vulnerability to RA [8].

2. Environmental factors
The environmental factors that include diet, smoking, obesity and infections trigger RA in

genetically predisposed individuals [9].

a) Cigarette smoking

There is a strong correlation between cigarette smoking and an elevated likelihood of acquiring RA as well as experiencing a more severe form of the illness. Smoking has the ability to stimulate the development of RF and ACPA, which are autoantibodies associated with the destruction of joints [10].

b) Periodontal Infections

Infection by Porphyromonas gingivalis which is a corner stone in periodontitis carries peptidyl arginine deiminase (PAD), an enzyme that has a role in the excessive citrullination of host proteins [11].

c) Viral Infections

The Epstein-Barr virus (EBV) is a major environmental contributor in developing of RA. Its structure has shown the existence of the QKRAA sequence inside the glycoprotein gp110, that is also encoded by the HLA-DRB1 gene. The immunological responses caused by molecular mimicry is a likely mechanism that contributes to RA [12].

d) Obesity and diet

There is a clear correlation between overweight and obesity with the development of RA and activity of the disease. A new meta-analysis has shown a heightened susceptibility to developing RA in those who are overweight or obese, as opposed to those who have a normal weight [13].

Pathogenesis of RA

The development of RA is intricate, including several kinds of cells, including macrophages, B and T cells, and dendritic cells, which invade the synovium [14]. CD4 T cells are the predominant lymphocyte population seen in the synovial infiltration. They secrete pro-inflammatory cytokines and work along with B-cells to produce antibodies [15].

Dendritic cells are crucial in initiating adaptive immune responses because they serve as antigen-presenting cells (APCs). This has been shown in the literature. There are 7 antigenic peptides that bind to T cells. CD4 T cells that have invaded the synovial tissue engage with dendritic cells. This connection leads to the activation of T cells through the interaction among the molecule CD28 on the T cell and its ligands CD80 and CD86, which are produced by APCs [16].

B lymphocytes are involved in seropositive RA, a condition where individuals produce autoantibodies that contribute to inflammation and destruction of tissues. Autoantibodies are produced by plasma cells, that undergo differentiation from B cells following interaction with CD4 T cells [17]. The activation of B cells necessitates the connection between CD40 ligand (CD40L) found on T cells and CD40 found on B cells. The interactions between IL-6 and B cells promotes the process of differentiation into plasma cells and facilitates the manufacture of antibodies, including ACPA [18].

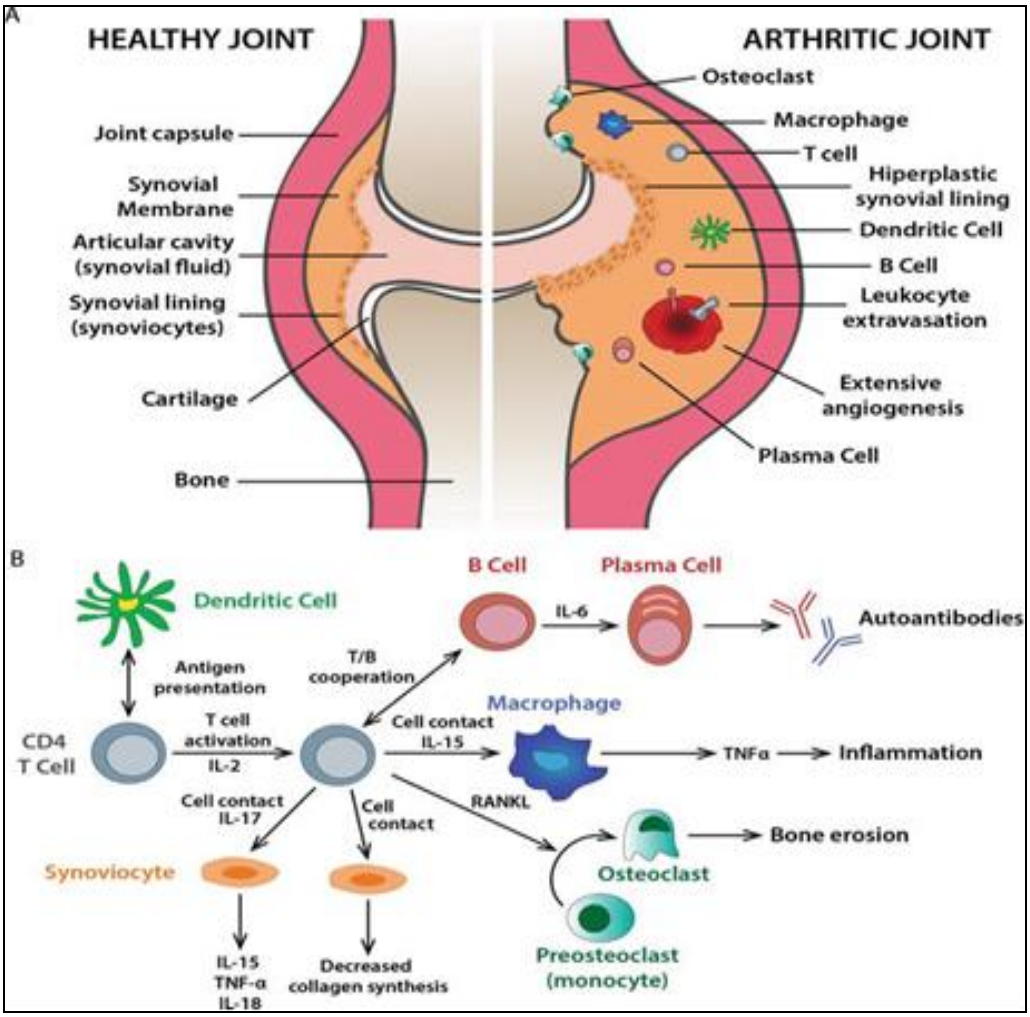

Fig 1: Pathogenesis of RA [19]

Ultrasound Scores

For assessing minor joints, it is recommended to use a high-resolution equipment equipped with a linear high-frequency probe ranging from 7.5 to 18 MHz. The score of synovitis was assessed using gray-scale ultrasonography (GSUS) and power-Doppler ultrasonography (PDUS) [20]. GSUS scores, which range from 0 to 3, are determined based on the extent of synovial hypertrophy in the joints according to the following criteria: Grade 0 indicates the absence of synovial hypertrophy, Grade 1 indicates a minor amount of synovial hypertrophy, Grade 2 indicates a moderate amount, and Grade 3 indicates a significant amount.

The PDUS scores were determined by evaluating the level of vascularity in the synovium of joints, using a scale ranging from 0 to 3. Grade 0 indicates the absence of Doppler activity. Grade 1 indicates little Doppler activity. Grade 2 indicates moderate, which is less than 50% of the background synovium. Grade 3 indicates severe, which is more than 50% of the background synovium.

Subjects were classified as having active synovitis if the GSUS was equal to or more than 2, or if the PDUS was equal to or greater than 1.

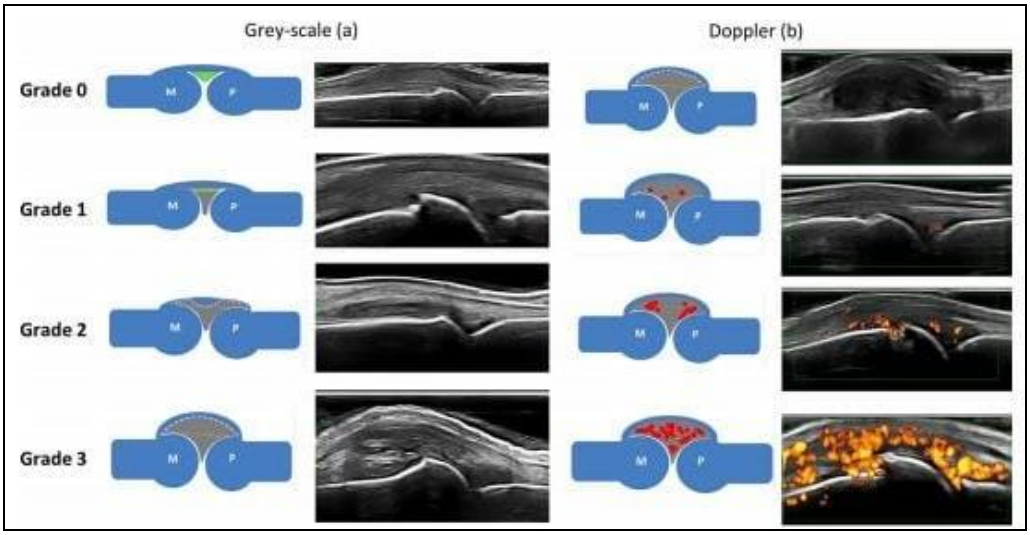

Fig 2: Grading of GSUS and PDUS [21]

Role of Musculoskeletal ultrasound in treatment of RA

The use of MSUS was more effective than clinical evaluation in identifying active inflammation. The ultrasound examination demonstrated a greater ability to identify subclinical inflammation in individuals with RA, as well as a better level of accuracy in ruling out inflammation among those who had tenderness but did not have swelling. This tool facilitates treatment determinations and maybe decreases the risk of overbearing therapy for patients [22].

MSUS can help clinicians to manage RA patients. Moreover, MSUS surpassed clinical examination in both diagnosing active illness and anticipating clinical responses to therapies or selecting appropriate treatment [23]. Incorporating a US evaluation into the care of individuals with inflammatory arthritis enhances the ability to forecast clinical outcomes. Adhering to imaging measurements for therapy leads to superior results compared to relying just on clinical objectives for treatment [24].

Ultrasound and prediction and assessment of joint damage

Identifying structural damage is crucial for predicting outcomes and may influence choices for future therapy. During the first stages of the illness, computed tomography (CT) may serve as the most reliable method for identifying the initial erosions. The drawbacks of CT scanning include the potential risk of radiation exposure, limited accessibility, and high expenses. MRI is able to identify even the tiniest erosions and observe bone marrow edema, which helps forecast the formation of erosions [25]. However, several articles have verified that the performance of the US is almost equivalent to that of MRI and CT in detecting erosions. PD US is a very accurate indicator of future joint deterioration in the afflicted joint. US is a very effective technique for identifying tiny and initial erosions in easily accessible joints, which include the metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints [26].

Recommended indications of MSUS

a) Patients with polyarthralgia and absence of overt signs of clinical synovitis

US is a valuable technique that may be used with clinical, biological, and traditional radiography data to confirm the existence of arthritis. US examination may identify unique imaging patterns that aid in clarifying the differential diagnosis [27].

b) Patients presenting with symptoms suggestive of rheumatoid arthritis, but without the necessary criteria for a definitive diagnosis

The chance of diagnosing RA rises as the number of afflicted joints rises. US may be utilized to determine the number of swollen joints. Only B-mode grade 2 synovitis, with or without PD activity, ought to be regarded relevant for the existence of synovitis [28].

c) Follow-up and assessment of individuals diagnosed with confirmed rheumatoid arthritis

The baseline US data are valuable for both disease monitoring and evaluating the prognostic significance of US in relation to other measures of activity of the disease [29].

Conclusion

MSUS is a safe, easy and useful tool for detection of subclinical synovitis and evaluation of disease activity. Combining ultrasonography with clinical evaluation may enhance the accuracy of diagnosing RA by recognizing synovitis more effectively than relying just on clinical examination. Ultrasonography enables Rheumatologists to increase their certainty in excluding a diagnosis of RA.

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